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FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/697,013	STANTON, VINCENT P.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *17-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group I, claims 1-16, in the response of September 5, 2003 is acknowledged.

Specification

2. The disclosure is objected to because of the following informalities:

A. The specification is objected to because the assigned SEQ ID NOs have not been used to identify each sequence listed, as required under 37 CFR §1.821(d). In particular, the sequence set forth in Table 2 should be accompanied by the appropriate sequence identifier (i.e., nucleotides 14701-37680 of SEQ ID NO: 5). Additionally, the description of figures 34 and 35 should include the sequence identifier for the sequences set forth in these figures or the figures themselves should be amended to include the sequence identifiers.

B. In claim 1, "present at least one polymorphic" should be amended to read "present at at least one polymorphic."

C. In claim 15, "mateched" should read "matched."

Claim Rejections - 35 USC § 101

3. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Definitions: [from UTILITY GUIDELINES TRAINING MATERIALS; repeated from http://www.uspto.gov/web/menu/utility.pdf]

"Credible Utility" - Where an applicant has specifically asserted that an invention has a particular utility, that assertion cannot simply be dismissed by Office personnel as being "wrong". Rather, Office personnel must determine if the assertion of utility is

credible (i.e., whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided). An assertion is credible unless (A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based is inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the applicant to support the assertion of utility. A *credible* utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use. For example, no perpetual motion machines would be considered to be currently available. However, nucleic acids could be used as probes, chromosome markers, or forensic or diagnostic markers. Therefore, the credibility of such an assertion would not be questioned, although such a use might fail the *specific* and *substantial* tests (see below).

"Specific Utility" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)
C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".
D. A method of making a material that itself has no specific, substantial, and credible utility.
E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

Note that "throw away" utilities do not meet the tests for a *specific* or *substantial* utility. For example, using transgenic mice as snake food is a utility that is neither specific (all mice could function as snake food) nor substantial (using a mouse costing tens of thousands of dollars to produce as snake food is not a "real world" context of use). Similarly, use of any protein as an animal food supplement or a shampoo ingredient are "throw away" utilities that would not pass muster as specific or substantial utilities under 35 U.S.C. ' 101. This analysis should, or course, be tempered by consideration of the context and nature of the invention. For example, it a transgenic mouse was generated with the specific provision of an enhanced nutrient profile, and disclosed for use as an animal food, then the test for specific and substantial *asserted* utility would be considered to be met.

"Well established utility" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art. "Well established utility" does not encompass any "throw away" utility that one can dream up for an invention or a nonspecific utility that would apply to virtually every member of a general class of materials, such as proteins or DNA. If this is the case, any product or apparatus, including perpetual motion machines, would have a "well established utility" as landfill, an amusement device, a toy, or a paper weight; any carbon containing molecule would have a "well established utility" as a fuel since it can be burned; any protein would have well established utility as a protein supplement for animal food. This is not the intention of the statute.
See also the MPEP at 2107 - 2107.02.

4. Claims 1-16 are rejected under 35 U.S.C. 101 because the claimed invention lacks a credible, substantial, specific or well-established utility.

The claims are drawn to methods for determining a genotype for ApoE comprising determining the nucleotide present at one or more polymorphic sites other than the sites at nucleotides 21250 and 21388 in an ApoE allele from an individual. The claimed methods are not supported by either a specific and substantial asserted utility or a well-established utility. The specification fails to provide objective evidence of any activity for the claimed nucleic acids containing polymorphisms and thereby any utility for the methods for detecting said polymorphisms. The specification (page 19) states that the claimed methods can be used for detecting genotypes or haplotypes as indicative of risk of a disease or condition, such as coronary heart disease, non-Alzheimer's neurological disease, Alzheimer's disease, stroke, or brain trauma. However, the specification has not established that the stated polymorphisms in the human ApoE gene are associated with any particular disease or condition. The specification provides information regarding the frequency of the polymorphisms in the population, but has not established that any of the polymorphisms are associated with a particular activity or condition in any specific population. The specification indicates that the genotypes can be used for selecting treatment for a disease or for determining the prognosis of a disease. However, the specification has not established a nexus between any disorders and any of the polymorphisms set forth in claim 2. The specification (page 20) further suggests that polymorphisms can be used to identify an individual. However, such a utility is general because it is a property of all polymorphisms and thereby is not considered to be a specific utility. The specification (page 21) also states that the polymorphisms can be used to determine whether a haplotypes is associated with a disease risk. It is stated that such a method would

require determining ApoE haplotypes for each individual in a set of individuals, dividing the set of individuals into at least two groups based on ApoE haplotypes and determining whether individuals in a group differ from individuals having a different ApoE haplotypes with respect to incidence, prevalence, severity, or progression of disease. However, such a utility is not considered to be substantial because it essentially involves performing research in order to find a utility for the polymorphisms, i.e., in order to establish that the polymorphisms are associated with disease. As stated in Brenner v. Manson, 383 U.S. 519 535-536, 148 USPQ 689, 696 (1966) " a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion". Support for an asserted utility that is specific and substantial would require, for example, a showing of a particular function for the ApoE polymorphisms, or a showing of a clear correlation between the disclosed polymorphisms and the occurrence of disease or an alteration in response to drug treatment. Merely identifying and studying the properties of the polymorphisms or performing assays to determine a correlation between the polymorphisms and disease does not constitute a "real world" context of use. Note, because the claimed invention is not supported by a specific and substantial asserted utility for the reasons set forth above, credibility has not been assessed. Neither the specification as filed nor any art of record discloses or suggests any property or activity for the nucleic acid compounds such that another non-asserted utility would be well established for the compounds. Accordingly, the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility. Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods which genotype the ApoE allele by detecting a polymorphism at position 17874, 18145, 21250 or 21388 of the ApoE gene of SEQ ID NO: 1, does not reasonably provide enablement for methods which genotype the ApoE allele by detecting any polymorphism in the ApoE gene or methods of genotyping which detect a polymorphism at position 16541, 16747, 16965, 17030, 17098, 17387, 17785, 17937, 18476, 19311, 20234, 21349, 23524, 23707, 23759, 23805, and 37237. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims are drawn to methods for determining a genotype for ApoE comprising determining the nucleotide present at one or more polymorphic sites other

than the sites at nucleotides 21250 and 21388 in an ApoE allele from an individual. The specification teaches a total of 19 polymorphisms in the ApoE gene, plus 2 additional polymorphisms at positions 21250 and 21388 which are characterized as being known in the art. The specification (see, for example, table 2) also teaches that the polymorphisms at positions 17874, 17937, 18145, and 18476 were previously described in the art. While a total of 19 polymorphisms in the ApoE gene have been described, this is not considered to be representative of the genus of any polymorphism in the ApoE gene "different from nucleotides 21250 and 21388." The ApoE gene is quite large, encompassing at least the 41,907 nucleotides set forth in SEQ ID NO: 1. While methods for amplifying DNA and sequencing are known in the art, extensive experimentation would be required to identify a representative number of polymorphisms within the claimed genus of any polymorphism in the ApoE gene. Claim 1 does not define the structure or nucleotide position for any of the polymorphisms to be detected. Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one

skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the state of the art indicates that it is unpredictable as to where additional polymorphisms would occur in the ApoE gene and what would be the identity of those polymorphisms. Further, such polymorphism can only be identified through random, trail-by-error experimentation.

Secondly, the specification has not taught one of skill in the art how to use each of the polymorphisms and thereby has not taught one of skill in the art how to use the methods of genotyping for the presence of these polymorphisms. Chartier-Harlin (US Patent No. 6,391,553) teaches that the Th1/E47cs (18145 polymorphism with respect to SEQ ID NO: 1) is associated with the occurrence of Alzheimer's Disease. The prior art also teaches that the polymorphism at position –491 (17874 of SEQ ID NO: 1) is associated with the occurrence of Alzheimer's disease. Accordingly, methods for detecting the polymorphism at positions 17874 and 18145 of SEQ ID NO: 1 are enabled. However, the specification has not adequately taught one of skill in the art how to use a method of determining a genotype of ApoE by detecting polymorphisms at positions 16541, 16747, 16965, 17030, 17098, 17387, 17785, 17937, 18476, 19311, 20234, 21349, 23524, 23707, 23759, 23805, and 37237 or any of the other undefined polymorphisms encompassed by the claims. The specification (page 19) states that the claimed methods can be used for detecting genotypes or haplotypes as indicative of risk of a disease or condition, such as coronary heart disease, non-Alzheimer's neurological disease, Alzheimer's disease, stroke, or brain trauma. However, the specification has not established that the polymorphisms set forth above are in fact associated with any

particular disease or condition. The specification provides information regarding the frequency of the polymorphisms in the population, but has not established that any of the polymorphisms are associated with a particular activity or condition in any specific population. The specification indicates that the genotypes can be used for selecting treatment for a disease or for determining the prognosis of a disease. However, the specification has not established a nexus between any disorders and any of the stated polymorphisms. The specification (page 20) further suggests that methods for determining a genotype by detecting a polymorphism can be used to identify an individual. However, such a use is considered to require additional experimentation because the specification has not established that any one particular polymorphism is correlated in a specific manner with a population of individuals and can be used in a predictable manner to identify an individual. The specification (page 21) also states that the polymorphisms can be used to determine whether a haplotypes is associated with a disease risk. It is stated that such a method would require determining ApoE haplotypes for each individual in a set of individuals, dividing the set of individuals into at least two groups based on ApoE halotypes and determining whether individuals in a group differ from individuals having a different ApoE haplotypes with respect to incidence, prevalence, severity, or progression of disease. Accordingly, such a method would require extensive experimentation.

Accordingly, in view of the unpredictability in the art in identifying new polymorphisms that can be used for practical purpose and the lack of specific teachings provided in the specification as to an association between the polymorphisms and any

particular disease or response to therapy and as to how to predictably identify additional polymorphisms in the ApoE gene, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

5. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods for determining a genotype for ApoE comprising determining the nucleotide present at one or more polymorphic sites other than the sites at nucleotides 21250 and 21388 in an ApoE allele from an individual. The specification teaches a total of 19 polymorphisms in the ApoE gene, plus 2 additional polymorphisms at positions 21250 and 21388 which are characterized as being known in the art. The specification (see, for example, table 2) also teaches that the polymorphisms at positions 17874, 17937, 18145, and 18476 were previously described in the art. While a total of 19 polymorphisms in the ApoE gene have been described, this is not considered to be representative of the genus of any polymorphism in the ApoE gene "different from nucleotides 21250 and 21388." The ApoE gene is quite large, encompassing at least the 41,907 nucleotides set forth in SEQ ID NO: 1. The specification also teaches the sequence of the ApoE gene. The specification contemplates that the polymorphisms can be used to detect diseases or conditions or response to therapy or to identify an individual. The specification also teaches the sequence of the ApoE gene (see SEQ ID NO: 1). However, the ApoE gene is quite

large, encompassing at least the 41,907 nucleotides set forth in SEQ ID NO: 1. While the specification has adequately described polymorphisms in the ApoE gene at positions 16541, 16747, 16965, 17030, 17098, 17387, 17785, 17937, 18145, 18476, 19311, 20234, 21349, 23524, 23707, 23759, 23805, and 37237 and thereby methods which detect said polymorphism meet the written description requirements of 35 U.S.C. 112, first paragraph, the specification does not disclose and fully characterize the genus of any polymorphism in the ApoE gene. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". In analyzing whether the written description requirement is

met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, 19 members of the very large genus of any ApoE polymorphisms claimed are identified by their complete structure, i.e. the location and identity of the polymorphism. It is then determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g., in terms of functional activity, or in terms of being in linkage disequilibrium with other well characterized polymorphisms, etc). In the instant case, no such identifying characteristics have been provided for any additional polymorphisms. The broadest reasonable interpretation of the claims indicates that the claims are inclusive of a huge genus of polymorphisms present at any position in the 41 Kb ApoE gene, including the promoter, 3' and 5' untranslated regions, exon and intron regions of the ApoE gene. While one could contemplate a nucleotide substitution at each and every position in the ApoE gene, such substitutions are not considered to be equivalent to specific polymorphisms and particularly to polymorphisms useful for a practical purpose, such as detecting risk of a disease. Rather, polymorphisms in the ApoE gene represent a distinct group of nucleotide variations which are expected to occur at only specific locations within the gene and consist of specific nucleotide alterations. Accordingly, knowledge of the sequence of the wild-type ApoE gene does not allow the skilled artisan to envision all of the contemplated polymorphisms encompassed by the claimed genus. Therefore, Applicants have not provided sufficient evidence that they were in possession, at the time of filing, of the invention as it is broadly claimed and thus the written description

requirement has not been satisfied for the claims as they are broadly written. Applicants attention is drawn to the Guidelines for the Examination of Patent Applications under 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-16 are indefinite. The claims are drawn to a method for determining the genotype for ApoE of an individual. However, the claims recite a single step of determining the nucleotide present at a polymorphic site. Accordingly, it is not clear as to whether the claims are intended to be limited to methods which determine the sequence of an ApoE gene at one or more polymorphic positions or if the method requires determining an individual's ApoE genotype.

Claims 1-16 are indefinite over the recitation of "nucleotides 21250 and 21388" and "nucleotides 16541...." because it is not clear as to which positions in the ApoE gene these nucleotides refer to since the claims do not provide a reference sequence that one could use to determine nucleotide positions. There are numerous sequences for ApoE available in the art and the claims do not state any particular ApoE sequence. Therefore, it is not clear as to whether the nucleotide positions are relative to those set forth in the sequence of SEQ ID NO: 5 or relative to some other unstated sequence.

Claims 6 and 7 are indefinite over the recitation of "the hybridizing species" because this phrase lacks proper antecedent basis.

Claim 8 is indefinite over the recitations of "the array" and "the hybridizing species" because these phrases lack proper antecedent basis.

Claim 9 is indefinite and confusing over the phrase "using a primer extension method distinguishing between nucleotides present at said at least one site" because it is not clear as to what is intended to be meant by this phrase. For example, it is unclear as to whether the primer extension reaction itself distinguishes between nucleotides or if the method of determining a genotype distinguishes between nucleotides. Furthermore, it is unclear as to which nucleotides are being distinguished, e.g., the different nucleotide positions or the different polymorphic variants that may be present at a single nucleotide position.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 are rejected under 35 U.S.C. 102(e) as being anticipated by Chartier-Harlin (US Patent No. 6,391,553).

Chartier-Harlin (see, for example, columns 2 and 6 and Figure 4) teaches a method for detecting a polymorphism in the ApoE gene and for genotyping the ApoE gene wherein the methods comprise determining the nucleotide sequence of the ApoE gene and identifying the presence of a specific polymorphism in the ApoE gene. In

particular, the reference (see, for example, column 8) teaches methods which determine the nucleotide at position 17874 (referred to as position –491 therein) and position 18145 (referred to as the Th1/E47cs polymorphism therein). The reference teaches that detection of the 17847 and 18145 polymorphisms can be used to facilitate the diagnosis of Alzheimer's disease. Chartier-Harlin also teaches detecting the polymorphisms that result in the Cys to Arg amino acid substitution at positions 112 and 158 of the ApoE protein (i.e., the 21250 and 21388 polymorphisms herein; see column 3). In the methods of Chartier-Harline, the polymorphisms are detected by amplifying the target nucleic acid by PCR and detecting the polymorphism in the amplified DNA using an allele specific hybridization probe (see, for example, column 6). Additionally, it is noted that the claims are broadly drawn to methods for determining a genotype for ApoE in an individual. The claims recite a single step of determining the nucleotide present at a polymorphic site in an ApoE gene from an individual. The recitation in the preamble does not result in a manipulative difference in the method steps when compared to the prior art disclosure. The claims are inclusive of methods which sequence the ApoE gene, as well as methods which detect any polymorphism in the ApoE gene. Since the method steps recited in the claims (i.e., determining the sequence of the APOE gene at position 17874 and 18145) are the same as those set forth by Chartier-Harlin, the claimed methods are anticipated by the disclosure of Chartier-Harlin.

8. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Chartier-Harlin (WO 99/01574).

Chartier-Harlin (see, for example, page 11-12 and Figure 4) teaches a method for detecting a polymorphism in the ApoE gene and for genotyping the ApoE gene wherein the methods comprise determining the nucleotide sequence of the ApoE gene and identifying the presence of a specific polymorphism in the ApoE gene. In particular,

the reference (see, for example, page 10-11 and 14) teaches methods which determine the nucleotide at position 17874 (referred to as position –491 therein) and position 18145 (referred to as the Th1/E47cs polymorphism therein). The reference teaches that detection of the 17847 and 18145 polymorphisms can be used to facilitate the diagnosis of Alzheimer's disease. Chartier-Harlin also teaches detecting the polymorphisms that result in the Cys to Arg amino acid substitution at positions 112 and 158 of the ApoE protein (i.e., the 21250 and 21388 polymorphisms herein; see page 5). In the methods of Chartier-Harline, the polymorphisms are detected by amplifying the target nucleic acid by PCR and detecting the polymorphism in the amplified DNA using an allele specific hybridization probe (see, for example, pages 18-19). Additionally, it is noted that the claims are broadly drawn to methods for determining a genotype for ApoE in an individual. The claims recite a single step of determining the nucleotide present at a polymorphic site in an ApoE gene from an individual. The recitation in the preamble does not result in a manipulative difference in the method steps when compared to the prior art disclosure. The claims are inclusive of methods which sequence the ApoE gene, as well as methods which detect any polymorphism in the ApoE gene. Since the method steps recited in the claims (i.e., determining the sequence of the APOE gene at position 17874 and 18145) are the same as those set forth by Chartier-Harlin, the claimed methods are anticipated by the disclosure of Chartier-Harlin.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5-10, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chartier-Harlin (US Patent No. 6,391,553).

The teachings of Chartier-Harlin are presented in paragraph 8 above. The reference teaches detecting the polymorphisms in the ApoE gene by performing allele specific hybridization. Chartier-Harlin does not teach detecting the ApoE polymorphisms using an array or a primer extension reaction.

Southern teaches methods for detecting polymorphisms/mutations in a gene wherein the methods comprising immobilizing an allele specific oligonucleotide on a solid support such as an array or bead (see columns 3 and 7). Southern (column 7) states that allele specific probes can be used to distinguish between allelic variants directly by hybridization. Sourthern also teaches that polymorphisms can be detected and distinguished from one another by primer extension methods in which a primer, immobilized on a solid support such as a bead or array, is extended one nucleotide using differentially labeled dideoxynucleotides and detected the extension product as a means of identifying the polymorphic nucleotide (columns 4 and 7-8).

In view of the teachings of Southern, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Chartier-Harlin so as to have immobilized the allele specific probes to a bead support or to have used an array of probes because this would have provided a rapid and effective means for simultaneously analyzing multiple mutations in the ApoE gene. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Chartier-Harlin so as to have detected the ApoE polymorphisms using the primer extension reaction disclosed by

Southern because this also would have provided an equally effective and rapid means for detecting polymorphisms in and genotyping the ApoE gene.

11. Claims 5-10, 14 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chartier-Harlin (WO 99/01574).

The teachings of Chartier-Harlin are presented in paragraph 9 above. The reference teaches detecting the polymorphisms in the ApoE gene by performing allele specific hybridization. Chartier-Harlin does not teach detecting the ApoE polymorphisms using an array or a primer extension reaction.

Southern teaches methods for detecting polymorphisms/mutations in a gene wherein the methods comprising immobilizing an allele specific oligonucleotide on a solid support such as an array or bead (see columns 3 and 7). Southern (column 7) states that allele specific probes can be used to distinguish between allelic variants directly by hybridization. Sourthern also teaches that polymorphisms can be detected and distinguished from one another by primer extension methods in which a primer, immobilized on a solid support such as a bead or array, is extended one nucleotide using differentially labeled dideoxynucleotides and detected the extension product as a means of identifying the polymorphic nucleotide (columns 4 and 7-8).

In view of the teachings of Southern, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Chartier-Harlin so as to have immobilized the allele specific probes to a bead support or to have used an array of probes because this would have provided a rapid and effective means for simultaneously analyzing multiple mutations in the ApoE gene. Furthermore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Chartier-Harlin so as to have detected the ApoE polymorphisms using the primer extension reaction disclosed by

Southern because this also would have provided an equally effective and rapid means for detecting polymorphisms in and genotyping the ApoE gene.

12. Claims 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chartier-Harlin (US Patent No. 6,391,553) or Chartier-Harlin (WO 99/01574) each further in view of Koster (US Patent No. 6,428,955).

The teachings of Chartier-Harlin (US Patent No. 6,391,553) are presented in paragraph 8 above and the teachings of Chartier-Harlin (WO 99/01574) are presented in paragraph 9 above. Each of the Chartier-Harlin references teach detecting the polymorphisms in the ApoE gene by performing allele specific hybridization. Chartier-Harlin does not teach detecting the ApoE polymorphisms using a cleavage assay.

Koster (see for example, columns 54-61) teachings genotyping ApoE using a cleavage reaction and detecting the size of fragments that result from chemical cleavage by mass spectrometry.

In view of the teachings of Koster, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Chartier-Harlin so as to have detected the polymorphisms in the ApoE gene using a cleavage assay and detecting the cleavage fragments by mass spectrometry because this would have provided an equally effective and rapid means for detecting polymorphisms in and genotyping the ApoE gene.

13. Claims 11 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chartier-Harlin (US Patent No. 6,391,553) or Chartier-Harlin (WO 99/01574) each further in view of Dahlberg (US Patent No. 5,719,028).

The teachings of Chartier-Harlin (US Patent No. 6,391,553) are presented in paragraph 8 above and the teachings of Chartier-Harlin (WO 99/01574) are presented in paragraph 9 above. Each of the Chartier-Harlin references teach detecting the

polymorphisms in the ApoE gene by performing allele specific hybridization. Chartier-Harlin does not teach detecting the ApoE polymorphisms using a cleavage assay.

Dahlberg (see for example, columns 8-10) teaches methods for detecting a polymorphism in a nucleic acid wherein the methods comprise performing a cleavase reaction.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Chartier-Harlin so as to have detected the polymorphisms in the ApoE gene using the cleavase detection method disclosed by Dahlberg because this would have provided an equally effective and rapid means for detecting polymorphisms in and genotyping the ApoE gene.

14. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chartier-Harlin (US Patent No. 6,391,553) or Chartier-Harlin (WO 99/01574) each further in view of Bamdad (US Patent No. 6541617).

The teachings of Chartier-Harlin (US Patent No. 6,391,553) are presented in paragraph 8 above and the teachings of Chartier-Harlin (WO 99/01574) are presented in paragraph 9 above. Each of the Chartier-Harlin references teach detecting the polymorphisms in the ApoE gene by performing allele specific hybridization. Chartier-Harlin does not teach detecting the ApoE polymorphisms using a cleavage assay.

Bamdad (see for example, columns 41-42 and 66) teaches methods for detecting a polymorphism in a nucleic acid wherein the methods comprise performing a hybridization reaction using FRET labels. In particular, Hayden teaches applying this detection method to identifying polymorphisms in the ApoE gene.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Chartier-Harlin so as to have detected the polymorphisms in the ApoE gene using the FRET labeling detection

method disclosed by Hayden because this would have provided an equally effective and rapid means for detecting polymorphisms in and genotyping the ApoE gene.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers
October 30, 2003

CARLA J. MYERS
PRIMARY EXAMINER